# Anaesthetic Strategy During Endovascular Therapy:

# General Anaesthesia or Conscious Sedation ?

## ("GOLIATH" – General Or Local anaestesia in Intra Arterial THerapy")

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Ischemic stroke is the third leading cause of death and the most common cause of acquired disability among adults in the western world. The only evidence-based therapy in acute ischemic stroke (AIS) is intra-venous (IV) tissue-plasminogen activator (tPA) also called thrombolysis (1). However, in patients with large artery stroke 50–70 % of all patients fail treatment with IV tPA due to recanalization failure (2). Removing the arterial occlusion has proven to be the best predictor of outcome. In addition, there is a significant proportion of patients in whom IV tPA is contraindicated. Under these circumstances endovascular therapy (EVT) with mechanical or pharmacological clot removal is the only treatment option.

Controversy exists whether general anaesthesia (GA) or conscious sedation (CS) should be used during EVT for acute ischemic stroke (AIS) (3,4). Currently there are no high quality randomised prospective trials addressing this question. Benefits of GA include airway protection, pain control and patient immobility for motion-free radiographic imaging and intervention. Conversely, GA is time consuming and possibly associated with longer time to revascularization and periods of hypotension with the risk of further ischemic injury (5,6). Advantages of CS might include shorter time to revascularization, fewer hemodynamic problems, the possibility for better neurological assessment during the procedure and possibly a faster procedure. The main arguments against CS are that patient movement can result in procedural complications, lack of airway control, higher

radiation dose and the need of more contrast media (5,6).

Recent retrospective studies have suggested that GA may worsen neurological outcome and increase mortality (7-11). However, National Institute of Health Stroke Score (NIHSS) was higher in the GA group, and GA was reserved for patients who could not cooperate and those with airway obstruction. None of the studies included a specific description of the criteria for selecting either GA or CS. Furthermore, systolic blood pressure below 140 mmHg appears to be related to worse outcome (9), but none of the retrospective studies present detailed blood pressure data. Thus, the level of evidence is low and to address this problem, patients subjected to EVT will be randomized to either GA or CS and their outcome will be followed.

As a standard procedure, Magnetic Resonance Imaging (MRI) will be performed before and after EVT. Outcome with respect to choice of anaesthetic regime is determined by changes in the modified Rankin scale (mRS) and infarct growth judged by MRI.

## Hypothesis

We hypothesize that patients receiving endovascular therapy under CS is associated with a better outcome, i.e. lower mRS and infarct size after EVT.

## Aim of the study

The main objective is to determine whether the use of GA or CS during endovascular clot removal in AIS patients influence patient outcome. Specifically, we will determine whether there is a difference in the primary and secondary outcome measures mentioned below.

The two groups will be compared in regards to:

*Primary outcome measures*

1. Growth of DWI lesion (infarct) on 48-72 hour follow up MRI (for all and for anterior strokes only).
2. Modified Rankin Score after 90 days

Secondary outcome measures

1. Time parameters
    a. Time from arrival at angiography suite to groin puncture
    b. Time from groin puncture to recanalization or end of procedure
    c. Time from arrival at angiography suite to recanalization or end of procedure
    d. Time from symptom onset to recanalization or end of procedure
2. Blood pressure variables:
    a. 20% drop in Mean Arterial Blood pressure (MABP) (relative to pre-induction MABP) during procedure
    b. MABP < 90 mmHg
    c. MABP < 70 mmHg
    d. Minutes with MABP < 70 mmhg
    e. Lowest and highest MABP during procedure
    f. Post-reperfusion MABP (measured immediately after reperfusion is obtained)
    g. Post procedure MABP (measured in recovery room)
3. Use of vasopressors (ephedrine/phenylephrine)
4. Complications
    a. Target vessel lesion (rupture, dissection)
    b. Access vessel dissection
    c. Clot migration to another, unaffected vascular territory
5. Other
    a. 24 hour NIHSS change
    b. Successful recanalization (mTICI 2b-3)
    c. Total radiation dose (DAB)
    d. Total amount of contrast media (ml)

In addition to the primary and secondary outcome measures we intend to register anesthetic complications related to conscious sedation and general anesthesia. This include: patient agitation/discomfort, need to convert to general anesthesia and airway management problems.

## Material and methods

Patients with ischemic stroke scheduled for acute EVT will be included in the study.

***Inclusion criteria:***

1) Severe stroke (NIHSS>=10)
2) mRS ≤2 before stroke
3) Groin puncture (arterial cannulation) feasible within 6 hours of symptom onset
4) MRI findings
    a. Clot in a reachable vessel. (ICA, ICA-T, M1, M2)
    b. Infarct volume <70ml on the initial scan

***Exclusion criteria***

1) MRI contraindications
2) GCS < 9
3) Patients intubated prior to arrival
4) Previous allergic reactions to anesthetics

***Anaesthesia protocol:***

*General anesthesia*: Rapid sequence intubation (Suxamethonium/alfentanil/propofol). Tracheal intubation and mechanical ventilation. Anaesthesia is maintained with propofol and remifentanil according to institutional guidelines

*Conscious Sedation*: The overall goal is to reduce agitation, anxiety, movements and still be able to communicate with the patient

1. Fentanyl bolus 25-50 ug. This dose may be repeated.

2. Propofol infusion. 1-2 mg/kg/h. If deemed necessary by the anesthesiologist the infusion rate can be increased or reduced

*Monitoring:*

Electrocardiography, pulseoximetry, end-tidal carbon dioxide and continuous invasive blood pressure measurements are performed during the procedure. The general goal is to maintain MABP ≥ 70 mmHg during the procedure (11). A reduction in MABP (< 70 mmHg) > 30 seconds is treated with vasopressors (ephedrine/phenylephrine)

***Data collection during the study:***

*Demographical data*: Age, gender, hypertension, diabetes mellitus, smoking, ischemic heart disease, known congestive heart failure, atrial fibrillation.

*Stroke data*: NIHSS, clot location (ICA, ICA-T, M1, M2), side (left, right). Infarct size before procedure (DWI), size of perfusion lesion (PWI), microbleeds, leucoaraiosis (Fazeka Scale) , recanalization (modified TICI score), infarct size after 24 hours, hemorrhagic transformation (HI-1, HI-2, PH-1, PH-2), 24 hour NIHSS, 90 day mRS.

*Time-related data*: Symptom onset/last seen well, time of admission, time of MRI scan, time to thrombolysis, time to arrival at angio-suite, time to groin puncture, time to recanalization, time to end of procedure.

*Data measured during procedure*: The need to convert to GA from CS (airway, agitation). Continuous invasive blood pressure. Blood pressure data are sampled continuously and stored on a laptop. The use of vasopressors (ephedrine/phenylephrine) will be recorded.

***Data analysis and statistics***

A power analysis showed that a sample size of *n* = 128 would be required in order to detect a 10 ml mean difference (SD 20 ml, alpha 0.05 and power of 0.8) in the volume of infarcted tissue between the GA and the LA group, respectively. We estimate it will take about 2 years to accomplish enrollment.

All data are entered into a database. Statistical analysis will be performed where we will compare the primary and secondary outcomes in the GA and LA groups.

## Ethics and consent

*Why should this study be conducted as an "Acute Study"*

The patients all suffer from a large ischemic stroke, which often involve a major part of the brain. Aphasia is a typical symptom at admission, which means that they are unable to speak and very often unable to understand any given information. If the right hemisphere is affected, the patients often present with severe neglect/anosognosia, meaning that they have no insight in their situation being in a state of disbelief and indifference to their symptoms. If the ischemic stroke involves the large arteries in the posterior part of the brain, the patients may have decreased consciousness and often appear in a comatose condition. Thus, the patients are unable to make crucial decisions.

Furthermore, the treatment has to be initiated very quickly. It is estimated that patients are losing 1.9 million brain cells per minute during a large vessel occlusion in the brain. The likelihood of a good outcome decreases with 10% every 30 minutes that passes.

Since the majority of the patients are incapacitated at admission and since the treatment is severely time dependent, we found that the conditions for an acute study are fulfilled.

## Consent

We will randomize to GA or CS without consent. Since there are no national or international guidelines as to weather GA or CS should be offered in this situation and since the focus of the study is to test two different anaesthesia procedures and not drugs, we do not find it necessary to obtain consent from patient or relative prior to EVT. The patients and their relatives will be informed that the patient will be offered EVT, which is our standard procedure.

After the procedure, the patient will be presented with a consent form with information about the study. We will ask for his acceptance to be in the study. The only thing that will differ for the patient being in the study, is the extra MRI scan to be performed 48-72 hours after the procedure. All other scans, tests and the follow-up are parts of our usual routine. The patient can withdraw consent anytime.

If the patient is in a state, where we cannot obtain consent, consent will be obtained from next of kin.

## Perspective

This randomized, prospective study will provide important data on whether outcome is influenced by the anesthetic technique during EVT. This knowledge may have great impact on the future choice of anesthetic technique during EVT of large vessel stroke.

## Dansk resume:

Blodprop i hjernen er en alvorlig sygdom, hvor der er stor risiko for død og/eller handicap. Den nuværende og eneste behandling med dokumenteret positiv effekt er trombolyse, hvor man indsprøjter kraftigt blodfortyndende medicin. Hvis der er tale om en stor blodprop er dette ofte ikke nok. I disse tilfælde kan man  fjerne blodproppen med et kateter i den lukkede pulsåre. Dette kaldes Endovaskulær Terapi (EVT). Dette har dog ikke vist sig at være bedre end medicinsk behandling i randomiserede undersøgelser.

I dette studie vil vi randomisere patienter, som vi ellers alligevel vil tilbyde EVT, til enten EVT under fuld bedøvelse (general anæstesi) eller under sedation, hvor patienten ligger og døser, men kan vækkes. Begge former for bedøvelse vil blive styret af anæstesiologer med særlig neuroanæstesiologisk kompetence

Vi vil opsamle data, der omfatter blodtryk, tidspunkt for de forskellige behandlingsmomenter, grad af handicap efter behandling samt volumen af skadet hjernevæv vurderet på MR scanning. Alle disse parametre registrerer vi i forvejen. Vi vil sammenligne det endelige omfang af skadet væv i hjernen hos patienter, der blev behandlet med de to forskellige bedøvelsesmetoder for at belyse om bedøvelsesmetoden påvirker behandlingsresultatet.

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Statistical Analysis Plan:

Statistical analyses

The primary analysis will be performed unadjusted and according to the intention-to-treat principle. This means that a cross-over patient from CS to GA will stay in the CS group for analysis. Data will be analyzed using conventional appropriate test statistics stratified according to NIHSS and age depending on the distribution of the individual outcome parameters (including paired t-test or Wilcoxon signed rank test for infarct volume and Mann–Whitney for mRS).

Supplementary analyses using multivariable regression will be done in order to account for any imbalances in the distribution of prognostic factors between the two treatment arms. A generalized linear mixed model will be used for comparing infarct growth in the two treatment arms. Ordinal and logistic regression will be used for comparing 90 days mRS. Univariate ($p<0.10$) predictors of infarct growth and 90 days mRS, respectively, will be included in the supplementary multivariable analyses. The association between MABP and mRS will be examined using multivariable polynomial regression.

Statistical significance is defined as a two-tailed $p<0.05$.